UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

Bracco Diagnostics, Inc., Plaintiff, v. Maia Pharmaceuticals, Inc., *et al.*, Defendants.	Civil Action No. 3:17-cv-13151 (PGS) (TJB) **MEMORANDUM AND ORDER**

SHERIDAN, U.S.D.J.

This matter comes before the Court on joint claim construction submitted by Plaintiff Bracco Diagnostics, Inc. ("Bracco") and Defendant Maia Pharmaceuticals, Inc. ("Maia") concerning United States Patent No. 6,803,046 (the "'046 Patent"). The '046 Patent is listed to market and sell the drug Kinevac® which is an injectable solution used for treating, preventing, and diagnosing gall bladder-related disorders. The parties dispute the meaning of three terms in the patent: (1) buffer; (2) surfactant/solubilizer; and (3) surfactant.

BACKGROUND

Kinevac was originally introduced in 1976 as a lyophilized white powder for parenteral (by injection) administration. The active ingredient in Kinevac is sincalide, a peptide molecule composed of eight amino acids bound together. ('046 Patent at 1:9-16). The patent also claims five other ingredients: at least one stabilizer, a surfactant/solubilizer, a chelator, a bulking agent/tonicity adjuster, and a buffer. (*Id.* at 37:41-49).

Kinevac currently has three uses approved by the FDA: (1) to stimulate gallbladder contraction; (2) to stimulate pancreatic secretion; and (3) to accelerate the transit of a barium meal through the small bowel. (*See* Declaration of Donald L. Rhoads ("Rhoads Decl."), Ex. 63, Labeling for Kinevac). Kinevac is a synthetic analog of a hormone produced by the human body known as CCK-8 (cholecystokinin). "CCK-8 acts on receptors within the gallbladder wall causing it to contract, cleaning out any remaining sludge or bile that may have accumulated within the gallbladder." ('046 Patent at 13:42-45). Kinevac "has a more rapid physiological effect on the gallbladder in terms of contraction and relaxation than the endogenous hormone (CCK-8)." (*Id.* at 13:49-51). Kinevac is "administered before and/or after diagnostic imaging . . . to improve visualization and/or diagnosis of various disease states." (*Id.* at 13:55-58). "Typically, the gallbladder contracts within 15 minutes after sincalide [(Kinevac)] injection and the hepatobiliary imaging agent . . . is injected 30 minutes later." (*Id.* at 14:17-20). Once the gallbladder is emptied it "is better able to take up and accumulate imaging agent . . . which helps to reduce the number of false positive studies." (*Id.* at 14:20-23).

As originally introduced, Kinevac suffered from some drawbacks. The '046 Patent identifies "potency variability" as one such drawback, which meant "a 20% overage of sincalide was required in previous sincalide formulations to compensate for the limitations of the bioassay." ('046 Patent at 1:27-40). The new invention "satisfie[d] the need for improved sincalide formulations by providing formulations that eliminate the need for a 20% overage of sincalide." (*Id.* at 1:43-45). "The sincalide formulations of the invention are also purer than prior art formulations, and have fewer degradants and more consistent potency." (*Id.* at 1:45-48).

The '046 Patent sets forth 108 total claims, which are directed to sincalide formulations (claims 1-20 and 106); methods for making sincalide formulations (claims 21-39); kits containing

sincalide formulations (claims 40-55 and 107-108); and methods for using sincalide formulations (claims 56-105). Claim 1 provides:

> A stabilized, physiologically acceptable formulation of sincalide comprising:
> (a) an effective amount of sincalide,
> (b) at least one stabilizer,
> (c) a surfactant/solubilizer
> (d) a chelator
> (e) a bulking agent/tonicity adjuster, and
> (f) a buffer.

('046 Patent at 37:41-49).

In August 2017, Maia filed a new drug application with the FDA seeking approval to market a sincalide product. The FDA granted the product priority review and then approved it in February 2018. In a notice letter required under the statute, Maia notified Bracco of several reasons that Maia argued its product does not infringe the '046 Patent:

- Maia's product does not include either a buffer or a surfactant/solubilizer.
- The amino acids in Maia's product are not used as buffers and have no buffering capacity over the pH range of Maia's formulation. An excipient[1] generally only provides a buffering capability when the pH of the formulation is within 1 pH unit of the excipient's pKa.
- The amino acids in Maia's product provide no surfactant or solubilizing effect because they do not have a suitable hydrophobic tail, and are not surface active by themselves, and do not function as solubilizers.
- Maia's product does not contain either polysorbate 20 or dibasic potassium phosphate.

[1] "Excipient" is used frequently in the briefs, but is not defined by the parties. I am using the ordinary meaning -- "An inactive substance that serves as the vehicle or medium for a drug or other active substance." See, Oxford English Dictionary.

Bracco filed this action pursuant to the Hatch-Waxman Act on December 15, 2017, claiming that Maia's proposed product infringes its claims in its '046 Patent. Maia challenges the validity of the asserted claims.

For the purposes of this hearing, the definition of three terms is at issue: (1) buffer, (2) surfactant/solubilizer; (3) surfactant. The following proposed definitions are proposed:

Term	Bracco's Proposal	Maia's Proposal
Buffer	Excipients that "stabilize the pH" and "include, but are not limited to, phosphoric acid, phosphate (e.g. monobasic or dibasic sodium phosphate, monobasic or dibasic potassium phosphate, etc.), citric acid, citrate (e.g. sodium citrate, etc.), sulfosalicylate, acetic acid, acetate (e.g. potassium acetate, sodium acetate, etc.), methyl boronic acid, boronate, disodium succinate hexahydrate, amino acids, including amino acid salts (such as histidine, glycine, lysine, imidazole), lactic acid, lactate (e.g. sodium lactate, etc.), maleic acid, maleate, potassium chloride, benzoic acid, sodium benzoate, carbonic acid, carbonate (e.g. sodium carbonate, etc.), bicarbonate (e.g. sodium bicarbonate, etc.), boric acid, sodium borate, sodium chloride, succinic acid, succinate (e.g. sodium succinate), tartaric acid, tartrate (e.g. sodium tartrate, etc.), tris(hydroxymethyl)-aminomethane, biological buffers (such as N-2-hydroxyethylpiperazine,N'-2-	A compound that stabilizes the pH of a sincalide formulation. **SOURCES**: '046 Patent at 9:44-47; Kilbanov Decl. at ¶¶ 92, 93, 95; Websters Ninth Collegiate Dictionary at 185 (1985); Webster's II New College Dictionary at 144 (1986); McGraw-Hill Dictionary of Scientific and Technical Terms at 278 (5th ed. 1994).

	ethanesulfonic acid (HEPES), CHAPS and other 'Good's' buffers), and the like." **SOURCES**: '046 Patent at 9:45-65, claims 3, 23, 41, 60, and 87, 9:65-10:9, Forrest Decl. at ¶¶ 31-62; Exs. 15-39.	
Surfactant/ solubilizer	Excipients that "may reduce the interfacial tension or aid in solubilization" and "include, but are not limited to, pluronics (e.g., Lutrol F68, Lutrol F127), Poloxamers, SDS, Triton-100, polysorbates such as TWEEN® 20 and TWEEN® 80, propylene glycol, PEG and similar compounds, Brij58 (polyoxyethylene 20 cetyl ether), cremophor EL, cetyl trimethylammonium bromide (CTAB), dimethylacetamide (DMA), NP-40 (Nonidet P 40), and N-methyl-2-pyrrolidone (Pharmasolve), glycine and other amino acids/amino acid salts and anionic surfactants containing alkyl, aryl or heterocyclic structures, and cyclodextrins." **SOURCES**: '046 Patent at 11:26-12:14; Forrest Decl. at ¶¶ 63-72.	A surfactant that is also a solubilizer. A solubilizer is a compound that aids in solubilization, thus preventing or reducing sincalide denaturation and/or degradation caused by peptide aggregation, precipitation, surface adsorption, or agitation at air/liquid or liquid/solid interfaces in solution. **SOURCES**: '046 Patent at 11:27-35, 11:51, claims 1, 6, 21, 26 Klibanov Decl. at ¶¶ 63, 64, 66-74.
Surfactant	Excipients that "may reduce the interfacial tension" and "include, but are not limited to, pluronics (e.g., Lutrol F68, Lutrol F127), Poloxamers, SDS, Triton-100, polysorbates such as TWEEN® 20 and TWEEN® 80, propylene glycol, PEG and similar compounds, Brij58 (polyoxyethylene 20	A compound that reduces the tension of the air/liquid or liquid/solid interface. **SOURCES**: '046 Patent at 11:29-34; Klibanov Decl. at ¶¶ 35-39, 43-48; Condensed Chemical Dictionary; Webster's Ninth Collegiate Dictionary; McGraw-Hill

	cetyl ether), cremophor EL, cetyl trimethylammonium bromide (CTAB), dimethylacetamide (DMA), NP-40 (Nonidet P-40), and N-methyl-2-pyrrolidone (Pharmasolve), glycine and other amino acids/amino acid salts and anionic surfactants containing alkyl, aryl or heterocyclic structures, and cyclodextrins." **SOURCES**: '046 Patent at 9:49-65, 11:26-36, claims 44, 63, 90; Forrest Decl. at ¶¶ 74-107.	Dictionary of Scientific and Technical Terms.

MARKMAN STANDARD

"It is a 'bedrock principle' of patent law that 'the claims of a patent define the invention to which the patentee is entitled the right to exclude.'" *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) (quoting *Innova/Pure Water Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1115 (Fed. Cir. 2004)). Claim construction determines the correct claim scope and is a determination exclusively for the court as a matter of law. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 978-79 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). The focus in construing disputed terms in claim language "is on the objective test of what one of ordinary skill in the art at the time of the invention would have understood the term to mean." *Id.* at 986.

To determine the meaning of the claims, courts start by considering the intrinsic evidence. *Phillips*, 415 F.3d at 1313; *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 861 (Fed. Cir. 2004); *Bell Atl. Network Servs., Inc. v. Covad Comms. Group, Inc.*, 262 F.3d 1258, 1267 (Fed. Cir. 2001). The intrinsic evidence includes the claims themselves, the specification, and the prosecution history. *Phillips*, 415 F.3d at 1314; *C.R. Bard, Inc.*, 388 F.3d at 861.

The court "begin[s] [its] analysis with the claim language itself." *Microsoft Corp. v. Multi-Tech Sys., Inc.*, 357 F.3d 1340, 1347 (Fed. Cir. 2004). The "claims 'must be read in view of the specification of which they are a part.'" *Phillips*, 415 F.3d at 1315 (quoting *Markman*, 52 F.3d at 979). "[T]he specification 'is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.'" *Id.* (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). This is true because a patentee may define his own terms, give a claim term a different meaning than the term would otherwise possess, or disclaim or disavow the claim scope. *Id.* at 1316. In these circumstances, the inventor's lexicography governs. *Id.* But, although "the specification often describes very specific embodiments of the invention," the Federal Circuit has "repeatedly warned against confining the claims to those embodiments." *Phillips*, 415 F.3d at 1323.

Buffer

The parties first disagree as to the definition of "buffer." Both claim their construction derives from the intrinsic evidence but also rely on some extrinsic evidence. As previously stated, Bracco urges the following definition:

> Excipients that "stabilize the pH" and "include, but are not limited to, phosphoric acid, phosphate (e.g. monobasic or dibasic sodium phosphate, monobasic or dibasic potassium phosphate, etc.), citric acid, citrate (e.g. sodium citrate, etc.), sulfosalicylate, acetic acid, acetate (e.g. potassium acetate, sodium acetate, etc.), methyl boronic acid, boronate, disodium succinate hexahydrate, amino acids, including amino acid salts (such as histidine, glycine, lysine, imidazole), lactic acid, lactate (e.g. sodium lactate, etc.), maleic acid, maleate, potassium chloride, benzoic acid, sodium benzoate, carbonic acid, carbonate (e.g. sodium carbonate, etc.), bicarbonate (e.g. sodium bicarbonate, etc.), boric acid, sodium borate, sodium chloride, succinic acid, succinate (e.g. sodium succinate), tartaric acid, tartrate (e.g. sodium tartrate, etc.), tris(hydroxymethyl)-aminomethane, biological buffers (such as N-2-hydroxyethylpiperazine,N'-2- ethanesulfonic acid (HEPES), CHAPS and other 'Good's' buffers), and the like."

(*See* Brief of Bracco, ECF No. 50 at 11). Maia proposes a much shorter definition: "A compound that stabilizes the pH of a sincalide formulation." (*See* Brief of Maia, ECF No. 50 at 30).

Accordingly, the parties generally agree that a buffer stabilizes pH. However, the critical difference is whether the phrase "of a sincalide formulation" should be included in the definition. Maia argues that buffer must be directed to sincalide formulations for two reasons: (1) the invention – as stated in the claims and specifications – is directed to sincalide formulations and (2) a compound, which may operate as a buffer in a formulation within a specific pH range, may not act as a buffer in formulations at different pH ranges (in other words, different buffers must be used for different pH values).

Bracco contends that its definition controls because it is taken directly from the intrinsic evidence and that additional language in the specifications should not be read as limiting the definition. *See Phillips*, 415 F.3d at 1323. Bracco further contends that the phrase "of a sincalide formulation" should not be read as limiting the definition of buffer because such a definition would imply that the buffer must stabilize the sincalide formulation when it is a final product.

Here, the patent holder substantially defined the buffer to certain ones set forth in the specifications and claims. *Astrazeneca AB, Aktiebolaget Hassle, KBI-E, Inc. v. Mutual Pharm. Co., Inc.*, 384 F.3d 1333, 1339 (Fed. Cir. 2004). "The specification acts as a dictionary 'when it expressly defines terms used in the claims or when it defines terms by implication.'" *Bell Atlantic Network Servs. v. Covad Comm. Gp., Inc.*, 262 F.3d 1258, 1268 (Fed. Cir. 2001). The applicant here set forth how the buffering agents are employed and provided an exemplary list of useful buffering agents. This list of buffers is sufficient to define the term in the context of the patent.

As such, reviewing claims 3, 23, 41, 60, and 87, which are nearly identical except that they are dependent on different independent claims, provide:

> [S]aid buffer is selected from the group consisting of phosphoric acid, phosphate, citric acid, citrate, sulfosalicylate, acetic acid, acetate, methyl boronic acid, boronate, disodium succinate hexahydrate, one or more amino acids, lactic acid, lactate, maleic acid, maleate, potassium chloride, benzoic acid, sodium benzoate, carbonic acid, carbonate, bicarbonate, boric acid, borate, sodium chloride, succinic acid, succinate, tartaric acid, tartrate, tris-(hydroxymethyl)aminomethane, and biological buffers.

('046 Patent at 37:51-60, 38:58-67, 39:63-40:5, 40:58-67, 42:18-27). However, citing many of the independent claims, Maia contends, "it is apparent that the context is a sincalide formulation." (Maia's Responsive Brief, ECF No. 57 at 28). For example, claim 1 references a "stabilized, physiologically acceptable formulation of sincalide." ('046 Patent at 37:41-42 (claim 1); *see also id.* at 38:39-40 (claim 20), 43:26-27 (claim 106)). Such a definition is far broader than the list of buffers cited in the specifications and claims. It is also noted that there are "preferred" buffers. A person skilled in the art (POSA) would rely on the list of buffers and the preferred buffers in particular. There is a caveat. Within the list set forth in Bracco's definitions, there are two catch-all phrases; "include but are not limited to" and "and the like" which are vague as to their scope. As such, those phrases are deleted because there is no teaching to the POSA as to what those phrases constitute.

Therefore, "buffer" is defined as:

- An excipient that: stabilizes the pH of sincalide formulations of the invention, and consequently, reduces the risk of chemical stability at extreme pH values. Buffering agents useful in the preparation of formulation kits of the invention include phosphoric acid, phosphate (e.g. monobasic or dibasic sodium phosphate, monobasic or dibasic potassium phosphate, etc.), citric acid, citrate (e.g. sodium citrate, etc.), sulfosalicylate, acetic acid, acetate (e.g. potassium acetate, sodium acetate, etc.), methyl boronic acid, boronate, disodium succinate hexahydrate, amino acids, including amino acid salts (such as histidine,

glycine, lysine, imidazole), lactic acid, lactate (e.g. sodium lactate, etc.), maleic acid, maleate, potassium chloride, benzoic acid, sodium benzoate, carbonic acid, carbonate (e.g. sodium carbonate, etc.), bicarbonate (e.g. sodium bicarbonate, etc.), boric acid, sodium borate, sodium chloride, succinic acid, succinate (e.g. sodium succinate), tartaric acid, tartrate (e.g. sodium tartrate, etc.), tris(hydroxymethyl) aminomethane, biological buffers (such as N-2-hydroxyethylpiperazine,N'-2- ethanesulfonic acid (HEPES), CHAPS and other 'Good's' buffers).

Surfactant

The parties next disagree as to the definition of "surfactant." Bracco proposes the following definition:

> Excipients that "may reduce the interfacial tension" and "include, but are not limited to, pluronics (e.g., Lutrol F68, Lutrol F127), Poloxamers, SDS, Triton-100, polysorbates such as TWEEN® 20 and TWEEN® 80, propylene glycol, PEG and similar compounds, Brij58 (polyoxyethylene 20 cetyl ether), cremophor EL, cetyl trimethylammonium bromide (CTAB), dimethylacetamide (DMA), NP-40 (Nonidet P-40), and N-methyl-2-pyrrolidone (Pharmasolve), glycine and other amino acids/amino acid salts and anionic surfactants containing alkyl, aryl or heterocyclic structures, and cyclodextrins."

Maia proposes a shorter definition: "A compound that reduces the tension of the air/liquid or liquid/solid interface."

By way of background, the patent for Kinevac suffers from potency variability, and the testing on which it was approved was of a guinea pig. The potency of the bioassay was unable to distinguish between the bioactivity of sincalide and the bioactivity of sincalide degradants. As a result, a 20% overage of sincalide was required in previous sincalide formulations to overcome the issues with the bioassay. As a result, there was a need for sincalide formulations "having improved and consistent potency as established by a sincalide specific assay such as HPLC."

The inventors were concerned with improving the potency and consistency of the formulations that was uncovered through experimentation. As such, what the experiments found was more important than the precise definition or function of a surfactant. Through experimentation, the inventors found that the preferred embodiments included excipients that perform the functions of at least (i) bulking agent/tonicity adjuster; (ii) a stabilizer; (iii) a surfacent; (iv) a chelator; and (v) a buffer. (Col. 5, L 15-20). As such, "a single expedient may perform more than one function." (Col. 4, L2 – 22-28). The specifications note that the peptides are susceptible to physical degradation through denaturation and other causes. As a result, the inventors found that "the addition of a nonionic surfactant such as polysorbate . . . may reduce interfacial tension (the purpose of the surfactant) or aid in solubilization, (the ability to be dissolved in water), thus preventing or reducing denaturation and/or degradation at air/liquid or liquid/solid interfaces of the product in solution." (Col. 11, L. 26-34). The problem which arises is that the specification and claims sometimes refer to "surfactant" and other times refer to "surfactant/solubilizers."

There are eight claims discussing the term "surfactant":

> 7. The formulation of claim 1, wherein said *surfactant* is a nonionic *surfactant*.
>
> 18. The formulation of claim 17, wherein said chelator is pentetic acid, said *surfactant* is polysorbate 20, said buffer is dibasic potassium phosphate, and said bulking agent/tonicity adjuster is D-mannitol.
>
> 27. The method of claim 21, wherein said *surfactant* is a nonionic *surfactant*.
>
> 38. The method of claim 37, wherein said chelator is pentetic acid, said *surfactant* is polysorbate 20, said buffer is dibasic potassium phosphate, and said bulking agent/tonicity adjuster is D-mannitol.
>
> 40. A kit comprising:
>
> (i) a powder mixture comprising

(a) sincalide,

(b) at least one stabilizer,

(c) a *surfactant*,

(d) a chelator,

(e) a bulking agent/tonicity adjuster, and

(f) a buffer;

(ii) a container to hold said powder mixture, and

(iii) optionally, a physiologically acceptable fluid.

63. The method of claim 56 wherein said *surfactant* is selected from the group consisting of anionic-*surfactants*, pluronics, poloxamers, SDS, Triton-100, polysorbates, propylene, glycol, PEG and similar compounds, Brij58 9poly (oxyethylene)20 cetyl ether, cremophor EL, cetyl trimethylammonium bromide (CTAB), dimethylacetamide (DMA), NP 40 (Nonidet P-40), and N-methyl-2-pyrrolidone (Pharmasolve), and amino acids.

90. The method of claim 77 wherein said *surfactant* is selected from the group consisting of anionic *surfactants*, pluronics, poloxamers, SDS, Triton-100, polysorbates, propylene, glycol, PEG and similar compounds, Brij58 9poly (oxyethylene)20 cetyl ether, cremophor EL, cetyl trimethylammonium bromide (CTAB), dimethylacetamide (DMA), NP 40 (Nonidet P-40), and N-methyl-2-pyrrolidone (Pharmasolve), and amino acids.

Although many of these are dependent claims, it should be noted that the independent claims that are referenced are formulations or methods that list surfactant as a component.

The specifications also address surfactants:

> Peptides are susceptible to physical degradations through denaturation, aggregation, precipitation, container surface adsorption and/or agitation induced denaturation. The addition of a nonionic *surfactant*, such as polysorbate, to the formulation, may reduce the interfacial tension or aid in solubilization thus preventing or reducing denaturation and/or degradation at air/liquid or liquid/solid interfaces of the product in solution.
>
> Surfactants/solubilizers include compounds such as free fatty acids, esters of fatty acids with polyoxyalkylene compounds

> like polyoxypropylene glycol and polyoxyethylene glycol;ethers of fatty alcohols with polyoxyalkylene glycols; esters of fatty acids with polyoxyalkylated sorbitan; soaps; glycerol-polyalkylene stearate; glycerol-polyoxyethylene ricinoleate; homo- and copolymers of polyalkylene glycols; polyethoxylated soya-oil and castor oil as well as hydrogenated derivatives; ethers and esters of sucrose or other carbohydrates with fatty acids, fatty alcohols, these being optionally polyoxyalkylated; mono-, di-, and triglycerides or soya-oil and sucrose; sodium caprolate, ammonium sulfate, sodium dodecyl sulfate (SDS), Triton-100 and anionic *surfactants* containing alkyl, aryl or heterocyclic structures.
>
> Examples of preferred surfactants/solubilizers for use in the present invention include, but are not limited to, pluronics (e.g., Lutrol F68, Lutrol F127), Poloxamers, SDS, Triton-100, polysorbates such as TWEEN® 80, propylene glycol, PEG and similar compounds, Brij58 (polyoxyethylene 20 cetyl ether), cremophor EL, cetyl trimethylammonium bromide (CTAB), dimethylacetamide (DMA), NP-40 (Nonidet P-40), and N-methyl-2-pyrrolidone (Pharmasolve), glycine and other amino acids/amino acids salts and anionic *surfactants* containing alkyl, aryl or heterocyclic structures, and cyclodextrins. TWEEN® is the most preferred *surfactant* in formulations of the invention.

('046 Patent at 11:29-63 (emphasis added)). In addition, example 3 of the patent indicates that during preliminary development, "it was observed . . . that the recovery of the active pharmaceutical ingredient, sincalide, in the bulk solution was sensitive to standing in open air." ('046 Patent at 19:56-61). Accordingly, "[t]o minimize sincalide degradation associated with surface absorption, surfactants are added as formulation excipients in bulk and lyophilized formulations of sincalide." (*Id.* at 20:5-9 emphasis added).

The specifications and claims adequately connote the meaning of "surfactant." That is, the purpose of adding this compound to the formulation is to "reduce the interfacial tension or aid in solubilization thus preventing or reducing denaturation and/or degradation at air/liquid or liquid/solid interfaces of the product in solution." ('046 Patent at 11:31-34). The specifications also indicate that a surfactant "minimize[s] sincalide degradation associated with surface adsorption." (*Id.* at 20:5-6).

Often extrinsic evidence is used "to better understand the underlying technology' and the way in which one of skill in the art might use the claim terms." *Phillips*, 415 F.3d at 1318 (quoting *Vitrionics*, 90 F.3d at 1583 .6). But the Court is mindful that the specification serves "as a check on the dictionary meaning of a claim term if the specification requires the court to conclude that fewer than all the dictionary definitions apply, or if the specification contains a sufficiently specific alternative definition or disavowal." *Id.* at 1320. F The parties rely on a definition from chemical dictionaries, and expert testimony explaining these definitions.

The Condensed Chemical Dictionary at 830 (9th Ed. 1977) includes a definition of "surface-active agent (surfactant)": "Any compound that reduces surface tension (q.v.) when dissolved in water or water solutions, or which reduces interfacial tension between two liquids, or between a liquid and a solid." Similarly, the McGraw-Hill Dictionary of Scientific and Technical Terms at 1960 (5th ed. 1994) defines "surface-active agent" as, "A soluble compound that reduces the surface tension of liquids, or reduces interfacial tension between two liquids or a liquid and a solid. Also known as surfactant." These dictionaries are consistent with the specifications in that each references a reduction of interfacial tension.

Expert testimony may also be considered when it "establish[es] that a particular term in the patent or the prior art has a particular meaning in the pertinent field." *Phillips*, 415 F.3d at 1318. Maia's expert, Professor Alexander M. Klibanov, stated that a POSA would understand a surfactant to be "a compound that reduces the tension of the air/liquid or liquid/solid interface." (Declaration of Alexander M. Klibanov ("Klibanov Decl."), ECF No. 49-1 at ¶¶ 14, 35). Klibanov explains that "claimed surfactants *must* exhibit a surfactant effect on sincalide formulations," (*id.* at ¶ 45), and "the patent requires a surfactant to confer an actual reduced interfacial tension to practice the claimed invention," (*id.* at ¶ 48).

Bracco's expert, Dr. Laird Forrest, opined that "a nonionic surfactant 'may reduce the interfacial tension,' which indicates to the person of skill in the art that a surfactant 'may', yet is not required to reduce surface tension." (Declaration of Laird Forrest ("Forrest Decl."), ECF No. 50-1 at ¶ 76). Forrest relies upon several treatises in support of this claim, including the following quote:

> A surfactant is . . . a substance that at low concentrations adsorbs at some or all of the interfaces in the system and significantly changes the amount of work required to expand those interfaces. Surfactants usually act to reduce interfacial free energy rather than to increase it, although there are occasions where they are used to increase it.

(Milton J. Rosen & Joy T. Kunjappu, Surfactants and Interfacial Phenomena at B0020619-22). Forrest also notes that Hackh's Chemical Dictionary "defines 'surfactant' as 'A surface-active substance, i.e., alters (usually reduces) the surface tension of water.'" (Forrest Decl. at ¶ 79). He contends "This definition . . . does not exclude and in fact includes increasing the surface tension as included in the definition of surfactant." (*Id.*). Forrest accordingly proposes the definition of surfactant urged by Bracco.

Unlike the exemplary list of buffers (see above), the exemplary list of surfactants proposed by Bracco may be broader than surfactants. In fact, the list proposed by Bracco begins with the statement, "Examples of preferred *surfactants/solubilizers* for use in the present invention". ('046 Patent at 11:51-52 (emphasis added)). Since the claims and specifications list surfactants/solubilizers separately from surfactants, it is more consistent to treat them separately here. As such, the list Bracco proposes is not adopted.

In short, Forrest's definition of a "surfactant" is more thorough and relies upon a more authoritative list of sources than Klibanov. The Court therefore finds the definition set forth in the specification is clear. The definition of surfactant is:

- An excipient that "may reduce the interfacial tension."[2]

Surfactant/Solubilizer

The parties next disagree as to the definition of "surfactant/solubilizer." Bracco proposes the following definition:

> Excipients that "may reduce the interfacial tension or aid in solubilization" and "include, but are not limited to, pluronics (e.g., Lutrol F68, Lutrol F127), Poloxamers, SDS, Triton-100, polysorbates such as TWEEN® 20 and TWEEN® 80, propylene glycol, PEG and similar compounds, Brij58 (polyoxyethylene 20 cetyl ether), cremophor EL, cetyl trimethylammonium bromide (CTAB), dimethylacetamide (DMA), NP-40 (Nonidet P 40), and N-methyl-2-pyrrolidone (Pharmasolve), glycine and other amino acids/amino acid salts and anionic surfactants containing alkyl, aryl or heterocyclic structures, and cyclodextrins."

Maia proposes, as a definition of "surfactant/solubilizer," "[a] surfactant that is also a solubilizer" and, as a definition of "solubilizer," proposes the following:

> A solubilizer is a compound that aids in solubilization, thus preventing or reducing sincalide denaturation and/or degradation cause by peptide aggregation, precipitation, surface absorption, or agitation at air/liquid or liquid/solid interfaces in solution.

Essentially, the difference between the two proposed definitions are that Bracco urges the Court to interpret the slash as meaning "and/or," whereas Maia proposes a definition where the excipient must be both a surfactant *and* a solubilizer.

In describing "surfactant/solubilizer," the specification notes that it "may reduce interfacial tension *or* aid in solubilization." ('046 Patent at 11:31-32 (emphasis added)). The "or" gives meaning to the use of the word "may." This indicates that the patent claims a surfactant and/or a solubilizer.

[2] Although this definition omits a portion of the sentence used in the patent, it is clear that the second half of that sentence – "or aid in solubilization" – refers to a solubilizer and not a surfactant.

Moreover, independent claim 1 refers in part to a "surfactant/solubilizer," and dependent claim 7 states, "The formulation of claim 1 wherein said nonionic surfactant is a polysorbate." ('046 Patent at 37:45, 38:6-7). If the Court were to accept Maia's position that claim 7 limits claim 1 to require both a surfactant and a solubilizer, it would render the use of "solubilizer" meaningless. Claim 7 is a narrower embodiment of claim 1 in that it focuses on a surfactant *rather than* a solubilizer. The Court therefore agrees with Bracco that "surfactant/solubilizer" should be interpreted as meaning surfactant and/or solubilizer.

Moreover, the specifications provide two separate exemplary lists, which are included within the definition of surfactant. The first list is not proposed by either party but a POSA would rely on this specification in formulating the product. The specifications state:

> Surfactants/solubilizers include compounds such as free fatty acids, esters of fatty acids with polyoxyalkylene compounds like polyoxypropylene glycol and polyoxyethylene glycol; ethers of fatty alcohols with polyoxyalkylene glycols; esters of farry acids with polyoxyalkylated sorbitan; soaps; glycerol-polyalkylene stearate; glycerol-polyoxyethylene ricinoleate; mono- and copolymers of polyalkylene glycols; polyethoxylated soya-oil and castor oil as well as hydrogenated derivatives; ethers and esters of sucrose or other carbohydrates with farry acids,. Fatty alcohols, these being optionally polyoxyalkylated; mono-, di-, and triglycerides of saturated or unsaturated fatty acids; glycerides or soya-oil and sucrose; sodium caprolate, ammonium sulfate, sodium dodecyl sulfate (SDS), Triton-100 and anionic surfactants containing alkyl, aryl or heterocyclic structures.

('046 Patent at 11:35-50). The second exemplary list is proposed by Bracco:

> Examples of preferred surfactants/solubilizers for use in the present invention include, but are not limited to, pluronics (e.g., Lutrol F68, Lutrol F127), Poloxamers, SDS, Triton-100, polysorbates such as TWEEN® 20 and TWEEN® 80, propylene glycol, PEG and similar compounds, Brij58 (polyoxyethylene 20 cetyl ether), cremophor EL, cetyl trimethylammonium bromide (CTAB), dimethylacetamide (DMA), NP-40 (Nonidet P 40), and N-methyl-2-pyrrolidone (Pharmasolve), glycine and other amino acids/amino acid salts and anionic surfactants containing alkyl, aryl or

heterocyclic structures, and cyclodextrins. TWEEN® 20 is the most preferred surfactant in formulations of the invention.

('046 Patent at 11:51-63).

Therefore, although the definition adopted by the Court is lengthy, it is consistent with the specifications in the patent. Thus, the Court adopts the following definition of surfactant/solubilizer:

- A surfactant and/or a solubilizer. The addition of a nonionic surfactant, such as polysorbate, to the formulation, may reduce the interfacial tension or aid in solubilization thus preventing or reducing denaturation and/or degradation at air/liquid or liquid/solid interfaces of the product in solution.

  Surfactants/solubilizers include compounds such as free fatty acids, esters of fatty acids with polyoxyalkylene compounds like polyoxypropylene glycol and polyoxyethylene glycol; ethers of fatty alcohols with polyoxyalkylene glycols; esters of fatty acids with polyoxyalkylated sorbitan; soaps; glycerol-polyalkylene stearate; glycerol-polyoxyethylene ricinoleate; mono- and copolymers of polyalkylene glycols; polyethoxylated soya-oil and castor oil as well as hydrogenated derivatives; ethers and esters of sucrose or other carbohydrates with fatty acids. Fatty alcohols, these being optionally polyoxyalkylated; mono-, di-, and triglycerides of saturated or unsaturated fatty acids; glycerides or soya-oil and sucrose; sodium caprolate, ammonium sulfate, sodium dodecyl sulfate (SDS), Triton-100 and anionic surfactants containing alkyl, aryl or heterocyclic structures.

  Examples of preferred surfactants/solubilizers for use in the present invention include, but are not limited to, pluronics (e.g., Lutrol F68, Lutrol F127), Poloxamers, SDS, Triton-100, polysorbates such as TWEEN® 20 and TWEEN® 80, propylene glycol, PEG and similar

compounds, Brij58 (polyoxyethylene 20 cetyl ether), cremophor EL, cetyl trimethylammonium bromide (CTAB), dimethylacetamide (DMA), NP-40 (Nonidet P 40), and N-methyl-2-pyrrolidone (Pharmasolve), glycine and other amino acids/amino acid salts and anionic surfactants containing alkyl, aryl or heterocyclic structures, and cyclodextrins. TWEEN® 20 is the most preferred surfactant in formulations of the invention.

ORDER

Having considered the written submissions of the parties and the documents attached thereto and having held a *Markman* hearing on this matter on July 9, 2019; for the reasons set forth herein and during the *Markman* hearing,

IT IS on this 2nd day of October, 2019;

ORDERED that the disputed term "buffer" is defined as follows:

- An excipient that: stabilizes the pH of sincalide formulations of the invention, and consequently, reduces the risk of chemical stability at extreme pH values. Buffering agents useful in the preparation of formulation kits of the invention include, phosphoric acid, phosphate (e.g. monobasic or dibasic sodium phosphate, monobasic or dibasic potassium phosphate, etc.), citric acid, citrate (e.g. sodium citrate, etc.), sulfosalicylate, acetic acid, acetate (e.g. potassium acetate, sodium acetate, etc.), methyl boronic acid, boronate, disodium succinate hexahydrate, amino acids, including amino acid salts (such as histidine, glycine, lysine, imidazole), lactic acid, lactate (e.g. sodium lactate, etc.), maleic acid, maleate, potassium chloride, benzoic acid, sodium benzoate, carbonic acid, carbonate (e.g. sodium carbonate, etc.), bicarbonate (e.g. sodium

bicarbonate, etc.), boric acid, sodium borate, sodium chloride, succinic acid, succinate (e.g. sodium succinate), tartaric acid, tartrate (e.g. sodium tartrate, etc.), tris(hydroxymethyl) aminomethane, biological buffers (such as N-2-hydroxyethylpiperazine,N'-2- ethanesulfonic acid (HEPES), CHAPS and other 'Good's' buffers);

ORDERED that the disputed term "surfactant" is defined as follows:

- An excipient that "may reduce the interfacial tension."

ORDERED that the disputed term "surfactant/solubilizer" is defined as follows:

- A surfactant and/or a solubilizer. The addition of a nonionic surfactant, such as polysorbate, to the formulation, may reduce the interfacial tension or aid in solubilization thus preventing or reducing denaturation and/or degradation at air/liquid or liquid/solid interfaces of the product in solution.

  Surfactants/solubilizers include compounds such as free fatty acids, esters of fatty acids with polyoxyalkylene compounds like polyoxypropylene glycol and polyoxyethylene glycol; ethers of fatty alcohols with polyoxyalkylene glycols; esters of fatty acids with polyoxyalkylated sorbitan; soaps; glycerol-polyalkylene stearate; glycerol-polyoxyethylene ricinoleate; mono- and copolymers of polyalkylene glycols; polyethoxylated soya-oil and castor oil as well as hydrogenated derivatives; ethers and esters of sucrose or other carbohydrates with fatty acids. Fatty alcohols, these being optionally polyoxyalkylated; mono-, di-, and triglycerides of saturated or unsaturated fatty acids; glycerides or soya-oil and sucrose; sodium caprolate, ammonium sulfate,

sodium dodecyl sulfate (SDS), Triton-100 and anionic surfactants containing alkyl, aryl or heterocyclic structures.

Examples of preferred surfactants/solubilizers for use in the present invention include, but are not limited to, pluronics (e.g., Lutrol F68, Lutrol F127), Poloxamers, SDS, Triton-100, polysorbates such as TWEEN® 20 and TWEEN® 80, propylene glycol, PEG and similar compounds, Brij58 (polyoxyethylene 20 cetyl ether), cremophor EL, cetyl trimethylammonium bromide (CTAB), dimethylacetamide (DMA), NP-40 (Nonidet P 40), and N-methyl-2-pyrrolidone (Pharmasolve), glycine and other amino acids/amino acid salts and anionic surfactants containing alkyl, aryl or heterocyclic structures, and cyclodextrins. TWEEN® 20 is the most preferred surfactant in formulations of the invention.

PETER G. SHERIDAN, U.S.D.J.